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# Stratifying Patients With Stroke in Trials That Target Brain Repair

Steven C. Cramer, MD

**Abstract**—A number of therapies are emerging that have the potential to reduce poststroke disability by promoting repair. Careful evaluation of patients with stroke might help distinguish those who are most likely to respond to a restorative therapy from those who lack biological substrate needed to achieve gains. Potential approaches to such stratification are considered, including measures of brain injury or of poststroke brain function. (*Stroke*. 2010;41[suppl 1]:S114-S116.)

**Key Words:** stroke ■ treatment ■ recovery ■ repair ■ stratify

An acute stroke initiates a number of events. Chief among these is brain injury, including the ischemic cascade, penumbra and its evolution, delayed neuronal loss, and apoptosis. However, a stroke also sets into motion a series of events related to repair. Within the first few days of an infarct, the brain initiates a number of processes related to restoration of function, such as increased expression of growth-associated genes, elevated levels of growth factors, angiogenesis, greater endogenous neural stem cell proliferation and migration, and increased dendritic arborization and synaptogenesis.<sup>1,2</sup>

These events represent biological targets for a class of therapies that fall under the rubric of brain repair. Although most patients show some degree of spontaneous behavioral improvement in the weeks-months after a stroke, this recovery is generally incomplete, and as a result stroke remains a major cause of human disability.<sup>3</sup> Brain repair therapies introduced during the days-weeks after stroke onset do not target neuroprotection; rather, such therapies aim to amplify innate repair mechanisms and thereby further improve behavioral outcomes after stroke. A growing literature also documents the ability of such interventions to improve behavioral status when introduced in the chronic phase, months-years after stroke, likely on the backbone of similar repair-based mechanisms.

A number of therapeutic classes are under investigation to promote brain repair after stroke.<sup>4</sup> The list includes growth factors, other large molecules such as monoclonal antibodies, stem cells, physiotherapy-based interventions, robotic devices, electromagnetic stimulation, neuroprosthetics, and small molecules. Small molecule approaches are wide-ranging and include drugs that modulate level of activity within specific neurotransmitter systems, vitamins, phosphodiesterase type 5 inhibitors, selective serotonin reuptake inhibitors, and more. The preclinical literature is blossoming with such studies, and many have been examined in human trials, including phase III trials in some cases.<sup>5,6</sup>

## Stratifying Stroke Patients to Optimize Prescription of Repair Therapies

Heterogeneity remains a major challenge for stroke research.<sup>7</sup> Currently, approved therapies for treating stroke are generally focused on the artery or the blood clot. Repair-based therapies that target neural tissue might, therefore, benefit from means to classify likely from unlikely treatment responders.

A key question is, therefore, how to optimally prescribe such repair-based therapies. Although poststroke repair trials to date have mainly relied on behavioral measures as key entry criteria,<sup>5,6,8,9</sup> patient selection might benefit from incorporation of measures that characterize the biological target, and do so in a manner that increases the likelihood of treatment effectiveness.

There are many levels with which this approach is currently taken in broader medical practice. For example, treatment decisions in myocardial disease are sometimes made by incorporating a measure of cardiac injury and viability.<sup>10</sup> Function of bronchiolar, adrenal, and other organs is probed to stratify patients and thereby define treatment. Specific measures of the biological target are sometimes used to direct treatment choices, such as when measuring breast cancer HER-2/neu antigen levels to decide on usage of trastuzumab or not.<sup>11</sup>

Details apart from patient selection can be learned. Thus, the amount, timing, or duration of therapy might also be informed by some measure of the targeted biological system. For example, in hypothyroidism, treatment is based on measures of serum TSH over weeks, rather than of hypothyroid symptoms over months.

How might these principles be applied to trials of repair-based therapies? A first step is to define valid, reliable measures of the biological system—measures that can be considered for use in stratifying patients with stroke. Such measures might consider brain systems in relation to injury, viability, function, or level of specific biological target, as these specific measures have proven fruitful elsewhere in medicine for optimizing treatment effects.

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Key clues regarding the best stratifying variables post-stroke come from studies of the natural history of stroke recovery in humans, such as can be found in measures of behavior, injury, or brain function. Candidate stratifying variables are listed below.

### Behavior

From a behavioral perspective, most patients show some spontaneous recovery after a stroke. Although spontaneous recovery generally evolves through characteristic stages, it can vary widely across neurological modalities<sup>12</sup> and across subjects. Nonetheless, measures exist that have good predictive value.<sup>13</sup> Individual variables such as medication use and social factors (eg, education or support systems) might also be important influences on degree of recovery.

### Injury

Many features of brain injury influence outcome after stroke. A perennial predictor is the total volume of injury. Location of injury is important, for example, injury to specific brain systems at times being more informative for clinical insight. For example, hand motor function after stroke is better explained by degree of injury to the hand motor map on motor cortex than by total volume of injury.<sup>14</sup> Injury can be defined using many different measures, including anatomic MRI, diffusion tensor imaging, neurophysiology, metabolic features, or spectroscopy.

### Function

A single stroke changes the function of multiple brain areas. Studies of this functional reorganization have found good concordance across multiple methods including functional MRI (fMRI), positron emission tomography, electroencephalography, magnetoencephalography, and transcranial magnetic stimulation. Thus, when primary cortical areas, or their key white matter tracts, are injured, their function is reduced and behavior declines. At the same time, compensatory brain events arise that appear to help maximize behavioral status, though clearly incompletely so. Multiple nodes in a distributed network increase activity toward driving behavior, and shifts arise in interhemispheric balance. Such patterns of functional reorganization of brain networks have been confirmed in multiple brain systems, including motor, sensory, language, and attention. In some cases, the structural counterpart to these reorganizational changes have been measured in parallel, such as the thickness of primary sensory cortex<sup>15</sup> or the size of residual corticospinal tract.<sup>16</sup>

The Table lists some specific candidate measures for stratifying patients based on the above approach. Each of these measures has been found to have value for distinguishing stroke subpopulations in relation to poststroke recovery. Many more measures can likely be added.

The goal is to use a stratifying measure that is derived from a biological model of the therapeutic intervention, and that is useful to distinguish patients across the model. A measure that has reliable predictive or stratifying value would be optimal; one whose measurements are sensibly related to a biological model generates maximum confidence. In this regard, note that several of the MRI techniques, such as fMRI

**Table. Candidates for Stratifying Patients in Repair-Based Trials**

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#### Demographics and medical history

Age

Chronic disease (eg, presence of diabetes mellitus)

#### Behavior

Global outcome measures<sup>21</sup>

Modality-specific outcome measures<sup>12</sup>

#### Affective state

Depression scales<sup>22</sup>

#### Brain function

Regional brain activation, including site, size, and magnitude<sup>23</sup>

Laterality<sup>24</sup>

Functional connectivity<sup>25</sup>

Resting state connectivity<sup>26</sup>

Metabolism<sup>27</sup>

Chemical state<sup>28</sup>

#### Injury

Regional fractional anisotropy<sup>29</sup>

Tractography (eg, from diffusion tensor imaging)<sup>16</sup>

Anatomic imaging<sup>15</sup>

#### Neurophysiology

Motor evoked potentials (eg, from transcranial magnetic stimulation)<sup>30</sup>

Electroencephalography<sup>31</sup>

#### Genetics

Single nucleotide polymorphisms (eg, BDNFVal<sup>66</sup>met)<sup>32</sup>

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and diffusion tensor imaging, and neurophysiological methods, such as transcranial magnetic stimulation, that are used to study human subjects have been directly applied to study animal models of stroke and its repair-based therapies. Studies that use the same methods to extract identical metrics across species are needed to clarify these biological models.

### Examples of Patient Stratification in Repair-Based Stroke Studies

Several examples have been published whereby bedside and functional neuroimaging measures have predictive value for treatment effects. In patients with chronic stroke, a smaller degree of ipsilesional primary motor cortex activation during an fMRI scan obtained at study baseline predicted gains from motor-related therapy, and did so more strongly than many other clinical or imaging metrics did.<sup>17</sup> Furthermore, patients who showed the highest gains from therapy also showed the largest boosts in motor cortex activation. The model suggests that patients who have intact but underused motor cortex resource can be trained to increase motor cortex activity, and that fMRI at baseline is providing a useful measure of the therapy's biological target. Stinear et al<sup>18</sup> achieved good success at predicting arm motor gains from therapy using diffusion tensor imaging-based measures of white matter integrity, transcranial magnetic stimulation (TMS)-based measures of motor system function, demographics, and behavioral status. The model suggests that therapy gains rely on an intact corticospinal tract, and that diffusion

tensor imaging and TMS at baseline provided a useful measure of this tract. This latter study emphasizes that multivariate approaches might have greater power than bivariate.

An approach in general medicine that might be instructive to stratification in repair trials is to use serial assessments before/after a challenge rather than simply obtaining a single cross-sectional assessment. Thus, whether assessing function of the myocardium, bronchioles, or adrenal glands, serial measurements before/after a challenge is often more informative than a singular basal measurement. Two studies suggest that this might be true in a repair-based trial, as a repeat fMRI measure midway through,<sup>19</sup> and a repeat TMS measure early into,<sup>20</sup> therapy can significantly distinguish those who will from those who will not respond well to subsequent intervention.

## Future Directions

Several preclinical, and some initial clinical, studies indicate the potential to improve outcome and reduce disability after stroke using approaches that focus on repair. Such therapies might have maximum effect if targeted toward the right patient subpopulations. Thus, once the best repair-based therapies are identified, major questions remain. For example, which are the subpopulations that are most likely to respond?; and by which means should such subpopulations be identified? A wide range of candidate tests exists for such patient stratification (Table). Initial studies<sup>17–20</sup> suggest the potential use of this approach, though these require independent verification and validation. Further study of the many factors that influence stroke recovery, both spontaneous and treatment-induced, will provide a means to best stratify patients seeking therapies that target brain repair. The issue of patient stratification might prove to be pivotal in maximizing effects of repair-based therapies.

## Disclosures

Dr Cramer has served as a consultant for GlaxoSmithKline, Pfizer, Photothera, Johnson & Johnson, Grupo Ferrer, and Allergan.

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